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Migraine and risk of haemorrhagic stroke in women: prospective cohort study

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ABSTRACT

Objectives To examine the association between migraine and migraine aura status with risk of haemorrhagic stroke.

Design Prospective cohort study.

Setting Women's Health Study, United States.

Participants 27 860 women aged ≥ 45 who were free from stroke or other major disease at baseline and had provided information on self reported migraine, aura status, and lipid values.

Main outcome measures Time to first haemorrhagic stroke and subtypes of haemorrhagic stroke.

Results At baseline, 5130 (18%) women reported any history of migraine; of the 3612 with active migraine (migraine in the previous year), 1435 (40%) described having aura. During a mean of 13.6 years of follow-up, 85 haemorrhagic strokes were confirmed after review of medical records. Compared with women without a history of migraine, there was no increased risk of haemorrhagic stroke in those who reported any history of migraine (adjusted hazard ratio 0.98, 95% confidence interval 0.56 to 1.71, $P=0.93$). In contrast, risk was increased in women with active migraine with aura (2.25, 1.11 to 4.54, $P=0.024$). The age adjusted increased risk was stronger for intracerebral haemorrhage (2.78, 1.09 to 7.07, $P=0.032$) and for fatal events (3.56, 1.23 to 10.31, $P=0.02$). Four additional haemorrhagic stroke events were attributable to migraine with aura per 10 000 women per year. Women who reported active migraine without aura had no increased risk for haemorrhagic stroke.

Conclusion Migraine with aura might, in addition to ischaemic events, also be a risk factor for haemorrhagic stroke. The relatively low number of events and attributable risk should caution against definitive conclusions and call for further confirmation of these observations.

INTRODUCTION

Migraine is an intermittent often severely disabling headache disorder that involves the neuronal and vascular system and has a prevalence of about 20% in middle aged women.¹⁻³ Up to a third of affected patients experience migraine aura, which is characterised by

transient neurological symptoms most often involving the visual system.

Several hospital and population based studies⁴⁻¹⁰ and meta-analyses^{11 12} have linked migraine, particularly migraine with aura, to an increased risk of ischaemic stroke. Potential explanations for this association include direct vascular involvement as part of the migraine pathophysiology,¹³ genetic poly morphisms,^{14 15} and shared risk factors, such as hypertension, smoking, raised cholesterol concentrations, and use of oral contraceptives.^{10 12 16} In addition, there is increasing evidence of pathology of the vessel wall in migraine, which might also increase the susceptibility to vascular events, including haemorrhagic stroke. Specifically, smooth muscle cell dysfunction,¹⁷ endothelial dysfunction,¹⁸⁻²⁰ and involvement of genotypes of the angiotensin converting enzyme¹⁵ and the endothelin receptor^{21 22} have been suggested.

Data on the association between migraine and haemorrhagic stroke, however, are sparse, mainly because of the generally low incidence of haemorrhagic strokes. Two case-control studies suggested an association,^{6 23} and a large population based study with health insurance data indicated an association between peripartum migraine and increased risk of intracerebral haemorrhage.²⁴

A previous report from the Women's Health Study did not find any association between migraine and increased risk of haemorrhagic stroke.⁷ After the association between migraine with aura and ischaemic vascular events became more apparent with longer follow-up,^{25 26} however, we re-evaluated the association of migraine and migraine aura status with haemorrhagic stroke after a mean of over 13 years of follow-up.

METHODS

We analysed data from participants in the Women's Health Study, a completed randomised trial designed to test the benefits and risks of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among apparently healthy women. The design, methods, and results have been described in detail previously.²⁷⁻²⁹ In brief, a total of 39 876 US female health professionals aged ≥ 45 years at baseline

(1993-6) and without a history of cardiovascular disease, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. Baseline information was self reported and collected by a posted questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. For the current analysis, we included follow-up information from the time of randomisation to 2 March 2009.

Before randomisation, blood samples were collected from 28 345 participating women and stored in tubes containing EDTA. Of these, 27 939 samples could be assayed for a full lipid profile (Roche Diagnostics, Basel, Switzerland). We excluded 79 women for whom we had no information on migraine, leaving 27 860 women free from any self reported vascular disease at baseline.

Assessment of migraine

On the baseline questionnaire, participants were asked: "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" We distinguished between women with no history of migraine and those who reported any history of migraine, active migraine (migraine in the year before the baseline questionnaire), or previous migraine (those who reported ever having had a migraine but none in the year before completing the questionnaire). Those participants who reported active migraine were also asked details about their migraine attacks, including duration of attack, unilateral location and pulsating quality of pain, interference with daily activities, aggravation by routine physical activity, nausea or vomiting, and sensitivity to light or sound. Women who reported active migraine were asked whether they had an "aura or any indication a migraine is coming." We used responses to classify affected women into active migraine with aura and active migraine without aura, as in other studies.^{7 25 30}

We have previously shown²⁵ that among participants in the Women's Health Study who reported active migraine, over 83% fulfilled all but one of the first edition International Classification of Headache Disorders³¹ criteria (code 1.7, migrainous disorder) and around 47% fulfilled all criteria (code 1.1 migraine without aura). We also showed that in a subsample of women from the Women's Health Study,³² according to second edition International Classification of Headache Disorders criteria,³³ in the 88% with self reported active migraine the diagnosis was migraine without aura (72%) or probable migraine without aura (16%).

Stroke ascertainment

We asked participants who reported a stroke on a follow-up questionnaire for permission to review their medical records. An endpoints committee of physicians, including a board certified vascular neurologist,

reviewed the medical records to confirm the diagnosis of stroke. Non-fatal stroke was confirmed if the participant had a new focal-neurological deficit of sudden or rapid onset attributable to a cerebrovascular event that persisted for more than 24 hours. Cases of fatal stroke were documented by evidence of a cerebrovascular cause of death obtained from all available sources, including death certificates and hospital records or information from next of kin. Clinical information and results from brain imaging were used to distinguish between major stroke subtypes, with excellent agreement between observers.³⁴ Cases of haemorrhagic stroke were further subdivided into intracerebral haemorrhages and subarachnoid haemorrhages. We did not include in our analyses instances of ischaemic stroke with secondary haemorrhagic transformation into the affected area. The rate of positive imaging results for the diagnosis of haemorrhagic stroke in the Women's Health Study was 97%.³⁵

Statistical analysis

We compared baseline characteristics of participants according to migraine status. We used analyses of covariance to adjust continuous measures and direct standardisation to adjust categorical variables and incidence rates for haemorrhagic stroke for age.

We used Cox proportional hazard models to calculate age and multivariable adjusted hazard ratios (with 95% confidence intervals) for the association of migraine and migraine aura status with haemorrhagic stroke and subtypes of haemorrhagic stroke. We tested the proportionality assumption of the model by including an interaction term for the categories of migraine with time and found no significant violation.

As the number of outcome events was relatively low compared with the number of potential confounders, we used two approaches for multivariable adjustment. Firstly, we built a model that included only a limited set of potential confounders (parsimonious model). This model included information on age (continuous), history of hypertension (blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic, or self reported diagnosis from a physician), smoking (never, past, current <15 cigarettes/day, ≥15 cigarettes/day), body mass index (BMI) (<25, 25-29.9, ≥30), alcohol consumption (rarely/never, 1-3 drinks/month, 1-6 drinks/week, ≥1 drink/day), and total cholesterol concentration (quarters of distribution).

Secondly, we used a propensity score³⁶ method to adjust for confounding. This allowed us to simultaneously adjust for a large number of covariates, which otherwise would not have been possible because of general modelling constraints.^{37 38} The propensity score is the estimated probability of exposure (that is, migraine status) given a set of covariates (that is, the potential confounders). We distinguished between a propensity score for any migraine and a propensity score for migraine with aura. To estimate the propensity score, we used a logistic regression model that included age (as before), systolic blood pressure (increments of 10 mm Hg), antihypertensive treatment,

smoking (as before), BMI (as before), alcohol consumption (as before), total cholesterol concentration (as before), exercise (rarely/never, less than once a week, once to three times a week, four or more times a week), menopausal status, postmenopausal use of hormone treatment (never, past, current), history of use of oral contraceptives, history of diabetes, family history of myocardial infarction before the age of 60, annual household income (<\$50 000 (£33 000, €40 000), \$50 000–<\$100 000, ≥\$100 000), highest level of education (less than university degree, university degree, masters degree, or doctorate), use of multivitamins (never, past, current), ethnicity (white versus other), interaction terms for age (<55, ≥55) with smoking, BMI, and oral contraceptive use, and randomised treatment assignments. Use of other lipid measures yielded comparable results. We weighted a Cox proportional hazards model based on propensity score values and used robust estimation of standard errors. We used standardised mortality ratio weights,^{39,40} which assign the value 1 for exposed and the propensity score odds for unexposed.

We incorporated an indicator variable for missing values if the number of women with missing information (maximum 1.9% missing) on potential confounding factors was 100 or more (this was the case for BMI and family history of myocardial infarction before the age of 60) or otherwise reassigned values of the reference group or past user group, as applicable.

In exploratory analyses, we evaluated potential effect modification of the association between migraine with aura (versus everybody else) and haemorrhagic stroke by age (<55, ≥55), history of hypertension (yes, no), smoking status (active, non-active), total cholesterol concentration (<6.2 mmol/l, ≥6.2 mmol/l), current postmenopausal hormone use (yes, no), estimated 10 year risk of coronary heart disease according to Framingham risk score (<5%, ≥5%),⁴¹ and randomised assignment to aspirin and vitamin E. Lastly, we ran a Cox proportional hazard model that adjusted for time varying frequency of non-steroidal anti-inflammatory drug (NSAID) intake and randomised aspirin assignment to explore the role of these drugs on the association between migraine with aura and haemorrhagic stroke.

All analyses were performed with SAS (SAS version 9.1, Cary, NC). All tests are two tailed, and we considered a $P < 0.05$ as significant.

RESULTS

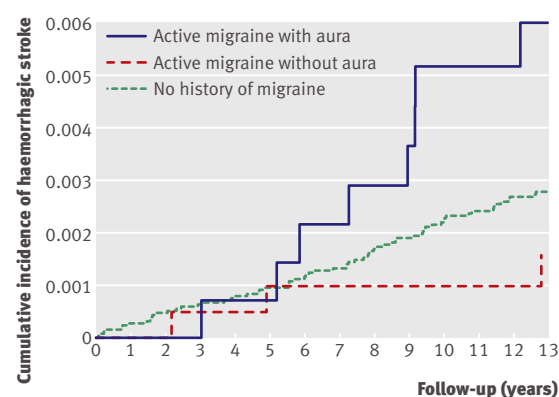
Of the 27 860 participating women, 5130 (18%) reported any history of migraine, of whom 3612 (70%) reported active migraine (migraine in the year before the baseline questionnaire) and 1518 (30%) indicated previous migraine. Of the women with active migraine, 1435 (40%) were classified as having migraine with aura. Table 1 summarises the age adjusted baseline characteristics of participants according to migraine and aura status. Compared with women without a history of migraine, those with active migraine with aura were younger, were less likely to

have a history of diabetes, smoked fewer cigarettes, and drank less alcohol. Women with migraine with aura were also more likely to be postmenopausal and to use postmenopausal hormones.

During a mean of 13.6 years of follow-up (377 711 person years), there were 85 confirmed haemorrhagic strokes (44 intracerebral haemorrhages, 36 subarachnoid haemorrhages, and five without a clear distinction). After adjustment for age, the incidence of haemorrhagic stroke per 10 000 women per year was 2.3 for those without migraine, 2.5 for those with any history of migraine, 6.3 for those with active migraine with aura, 0.8 for those with active migraine without aura, and 1.3 for those who reported previous migraine. Compared with women without migraine, after adjustment for age and an assumption of causality, there were four additional haemorrhagic stroke events associated with migraine with aura per 10 000 women per year.

Table 2 summarises the age and multivariable adjusted hazards ratios for the association between migraine and risk of haemorrhagic stroke. Compared with women who did not report history of migraine, those who reported any history had no increased risk of haemorrhagic stroke (age adjusted hazard ratio 1.04, 95% confidence interval 0.59 to 1.82, $P = 0.90$). When we made a distinction with regard to migraine aura, however, the results differed. After adjustment for age and compared with women without migraine history, women with active migraine with aura had increased risk of haemorrhagic stroke (2.31, 1.15 to 4.64, $P = 0.019$). Adjustment for age, history of hypertension, smoking, BMI, alcohol consumption, and total cholesterol concentration (parsimonious model) yielded similar results. Also, adjustment for a large number of covariates via a regression model weighted for a propensity score did not substantially attenuate this finding (2.25, 1.11 to 4.54, $P = 0.024$). Women who reported active migraine without aura and those who reported previous migraine had no increased risk of haemorrhagic stroke.

The figure shows the age adjusted incidence rates for haemorrhagic stroke for women without a history of migraine, women with active migraine with aura, and



Age adjusted cumulative incidence of haemorrhagic stroke according to migraine in women

Table 1 | Age adjusted baseline characteristics according to migraine status in Women's Health Study (n=27 860). Figures are percentages of women* unless stated otherwise

Characteristics	No migraine history	Active migraine		Previous migraine†
		With aura	Without aura	
No of participants	22 730	1435	2177	1518
Mean (SE) age (years)	54.9 (0.05)	53.2 (0.16)	52.6 (0.12)	55.5 (0.19)
Mean (SE) total cholesterol (mmol/l)	5.5 (0.01)	5.5 (0.03)	5.5 (0.02)	5.6 (0.03)
Mean (SE) BMI	25.9 (0.03)	25.8 (0.13)	26.2 (0.11)	26.1 (0.13)
History of hypertension‡	24.6	25.5	26.0	30.4
Antihypertensive treatment	13.0	13.9	14.3	17.2
History of diabetes	2.5	1.8	1.6	2.7
Smoking:				
Never	51.3	52.6	56.3	50.6
Past	37.0	37.3	34.5	35.4
Current <15 cigarettes	4.4	3.9	3.5	5.2
Current ≥15 cigarettes	7.3	6.2	5.8	8.9
Alcohol consumption:				
Rarely/never	43.5	48.3	47.4	45.1
1-3 drinks/month	13.1	13.1	15.5	14.2
1-6 drinks/week	32.7	30.3	30.1	30.4
≥1 drink/day	10.8	8.3	7.1	10.3
Physical activity:				
Rarely/never	37.0	38.2	39.4	39.1
<1/week	19.2	20.5	21.7	20.1
1-3/week	32.3	30.7	29.2	29.4
≥4/week	11.6	10.6	9.7	11.3
Premenopausal	28.1	23.9	26.2	25.0
Current postmenopausal hormone use	41.7	51.0	46.7	43.7
Family history of myocardial infarction before age 60	12.6	14.3	13.0	13.8
Use of multivitamins	13.1	13.2	11.2	11.5
Randomised to aspirin	50.2	49.1	50.5	47.8
Randomised to vitamin E	50.1	51.5	48.1	50.0

*Proportions might not add up to 100% because of rounding or missing values.

†History of migraine but no active migraine in year before completion of baseline questionnaire.

‡Systolic blood pressure ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or self reported diagnosis from physician.

those with active migraine without aura. Compared with women with no history of migraine, the increased rates of haemorrhagic stroke for women with active migraine with aura were more apparent towards later years of follow-up.

To evaluate the association of migraine with aura with the few subtypes of haemorrhagic stroke (intracerebral haemorrhage n=44; subarachnoid haemorrhage n=36) as well as with fatal haemorrhagic stroke (n=28), we combined women who did not report migraine, reported migraine without aura, and reported previous migraine to form a reference group. The association between active migraine with aura and haemorrhagic stroke was stronger for intracerebral haemorrhages (hazard ratio adjusted for age 2.78, 1.09 to 7.07, P=0.032) than for subarachnoid haemorrhages (1.73, 0.53 to 5.65, P=0.37) and stronger for fatal (3.56, 1.23 to 10.31, P=0.02) than non-fatal haemorrhagic stroke (1.96, 0.78 to 4.93, P=0.15).

With regard to potential effect modification of the age adjusted association between active migraine with aura and haemorrhagic stroke, we found stronger

effect estimates for age 55 and above (3.80, 1.61 to 8.97), no history of hypertension (3.23, 1.45 to 7.20), cholesterol concentrations <6.2 mmol/l (2.86, 1.36 to 6.01), current use of postmenopausal hormones (2.84, 1.19 to 6.76), non-active smokers (2.70, 1.29 to 5.67), Framingham risk score estimates of coronary heart disease of <5% (2.98, 1.41 to 6.30), randomisation to vitamin E (2.87, 1.21 to 6.80), and randomisation to aspirin placebo (3.27, 1.26 to 8.49). We did not, however, find any significant effect modification (smallest P value 0.19 for the interaction by age).

When we ran age adjusted Cox proportional hazards models that controlled for time varying frequency of NSAID use during the trial period and randomised aspirin assignment, there was no attenuation in the hazard ratio for haemorrhagic stroke for women with migraine with aura (2.34, 1.17 to 4.70).

DISCUSSION

In this prospective study of middle aged and initially apparently healthy women, we found an association between migraine with aura and an increased risk of

haemorrhagic stroke. Compared with women with no history of migraine and after adjustment for many potential confounders through a propensity score weighting, women who reported active migraine with aura had over twice the risk of haemorrhagic stroke. The low number of haemorrhagic strokes and the relatively low attributable risk, however, should caution against definitive conclusions about the association. Women who reported active migraine without aura or migraine in the more distant past had no increased risk of haemorrhagic stroke.

Our findings extend previous observations from the Women's Health Study of an association between migraine with aura and increased risk of ischaemic vascular events, including ischaemic stroke, myocardial infarction, coronary revascularisation, angina, and death from ischaemic cardiovascular causes.²⁵ The magnitude and pattern of the association between migraine with aura and haemorrhagic stroke are similar to those of migraine with aura and ischaemic vascular events. In contrast with the association between migraine with aura and ischaemic stroke, which is stronger among younger individuals,⁷ the association with haemorrhagic stroke seems more apparent in the older age group. We did not, however, find a significant effect modification.

Comparison with other studies

Our data contrast with a previous report from the Women's Health Study in which migraine with aura was not associated with increased risk of haemorrhagic stroke after a mean of nine years of follow-up.⁷ The pattern of association suggests that this discrepancy is caused by the difference in length of follow-up. The increased risk for haemorrhagic stroke among women with migraine with aura becomes apparent only after longer follow-up (mean of 13.6 years in the present study), similar to a pattern observed for ischaemic vascular events.^{25 26}

While several studies^{4-8 23 42} and two meta-analyses^{11 12} have evaluated the association of migraine, and specifically migraine with aura, with ischaemic stroke, data on the association between migraine and haemorrhagic stroke are sparse. One case-control study found an

increased risk of haemorrhagic stroke for people with a family history of migraine (odds ratio 2.30, 95% confidence interval 1.35 to 3.90), but in those with active migraine the increased risk was more apparent for people with migraine without aura (1.84, 0.77 to 4.39).⁶ Another study of 430 women aged 15-44 with stroke used two control groups (their matched neighbours and hospital controls) to evaluate the association between migraine and haemorrhagic stroke.²³ Compared with the neighbour control group, women with migraine who did not use oral contraceptives had an increased risk of haemorrhagic stroke (1.8, 1.2 to 2.7). The increased risk was not apparent when the hospital control group was used as reference, which might relate to biases when using hospital based control populations. Women with migraine who additionally used oral contraceptives had a significantly increased risk of haemorrhagic stroke regardless of the control group used for comparison.²³ Information on migraine aura was not available in this study. In a large population based sample of inpatients, ICD-9 coding for migraine in the perinatal period was associated with various vascular events, including intracerebral haemorrhage (9.1, 3.0 to 27.8).²⁴

Potential mechanisms linking migraine with haemorrhagic stroke

In addition to previous studies that have identified migraine with aura as a marker of ischaemic vascular events, our data suggest that it is also a marker of increased risk of haemorrhagic stroke. Potential mechanisms by which migraine with aura could be linked with increased risk of haemorrhagic stroke, however, are currently speculative. There could be several potential links. Firstly, one link might involve dysfunction or pathology of the vessel wall, which is supported by studies reporting smooth muscle cell dysfunction¹⁷ and endothelial dysfunction in migraine^{18 20} as well as pathological vascular resistance, already apparent in young people with migraine.¹⁹ This could ultimately increase the risk of intracerebral haemorrhage as well as the risk of lacunar infarcts.⁴³ Secondly, there might be a synergistic effect between the vascular dysfunction in migraine and additional risk factors for haemorrhagic stroke. Previous results have suggested that the

Table 2 | Hazard ratios (95% confidence intervals) for haemorrhagic strokes adjusted for age, multivariables, and propensity score according to migraine status in Women's Health Study (n=27 860)

	No migraine history (n=22 730)	Any history of migraine (n=5130)	Active migraine		Previous migraine* (n=1518)
			With aura (n=1435)	Without aura (n=2177)	
No with haemorrhagic stroke (n=85)	70	15	9	3	3
Age adjusted	1.00	1.04 (0.59 to 1.82), P=0.90	2.31 (1.15 to 4.64), P=0.019	0.52 (0.16 to 1.66), P=0.27	0.63 (0.20 to 1.99), P=0.43
Multivariable adjusted (parsimonious) model†	1.00	1.03 (0.59 to 1.81), P=0.91	2.34 (1.16 to 4.70), P=0.017	0.54 (0.17 to 1.72), P=0.29	0.59 (0.19 to 1.88), P=0.37
Propensity score adjusted‡	1.00	0.98 (0.56 to 1.71), P=0.93	2.25 (1.11 to 4.54), P=0.024	0.49 (0.14 to 1.70), P=0.26	0.45 (0.14 to 1.48), P=0.19

*History of migraine but no active migraine in year before completion of baseline questionnaire.

†Adjusted for age, history of hypertension, smoking, BMI, alcohol consumption, and total cholesterol concentration.

‡One propensity score calculated for overall migraine and one for having migraine with aura. Both models included information on age, systolic blood pressure, use of antihypertensive medication, smoking, BMI, alcohol consumption, exercise, total cholesterol concentration, postmenopausal status, postmenopausal hormone use, history of oral contraceptive, history of diabetes, family history of myocardial infarction before age 60, annual household income, level of education, multivitamin use, ethnicity, randomised treatment, and interaction terms for age with smoking, BMI, and oral contraceptives. Hazard ratios estimated by weighted Cox proportional hazard models.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Migraine with aura has been associated with increased risk of ischaemic stroke and other ischaemic vascular events

Migraine with aura has also been linked to an adverse cardiovascular risk profile and endothelial dysfunction

WHAT THIS STUDY ADDS

In a large prospective study of female health professionals aged 45 years or older at study entry, migraine with aura was associated with increased risk of haemorrhagic stroke

Absolute numbers and attributable risk were low, arguing against definitive conclusions, and calling for further confirmation of these observations

association between migraine with aura and ischaemic stroke is strongest among individuals with a low risk of vascular events³⁰ as measured by the Framingham risk score for coronary heart disease, a pattern that is also suggested for haemorrhagic stroke in our data. Thirdly, both migraine and intracerebral haemorrhage could be related to a common cause, such as arteriovenous malformations,⁴⁴ but such malformations are only a rare cause of migraine. Fourthly, migraine has been linked to platelet dysfunction,⁴⁵ which could lead to an increased susceptibility to bleeding. Most studies, however, point towards an activation of the coagulation cascade,^{18,46} and there is no evidence of a generalised increased risk of bleeding among people with migraine. Finally, use of pain medication that inhibits platelet aggregation, such as aspirin and NSAIDs, could increase the risk of haemorrhagic stroke among patients with migraine. We believe this is an unlikely explanation of our findings as such medications are used by patients with migraine both with and without aura; in addition, the association between migraine with aura and haemorrhagic stroke in our study was stronger among those randomised to an aspirin placebo. Furthermore, when we adjusted for time varying NSAID use and randomised aspirin assignment the results were unchanged.

Strengths and limitations

Our study has several strengths, including its large sample size, haemorrhagic stroke cases confirmed by an endpoints committee of physicians with high agreement between raters in the classification of major subtypes of stroke,³⁴ and homogeneity of the study participants, which should reduce confounding. Furthermore, we used a propensity score technique that allowed us to control for a large number of potential confounders, including socioeconomic and lifestyle factors that might play a role in the occurrence of haemorrhagic stroke^{47,48} and that have also been linked with migraine.^{49,50}

Several limitations should, however, be considered. Firstly, and most importantly, the number of cases of haemorrhagic stroke was small ($n=85$) and only nine cases occurred among women with active migraine with aura. Thus, and despite statistical significance, our data should be interpreted with caution. Secondly, migraine status was self reported by participants and

not classified according to strict International Headache Society criteria.³³ Although previous reports from the Women's Health Study have shown good agreement of migraine classification with modified International Headache Society criteria,^{25,26} misclassification is possible. As our study design is prospective, however, such misclassification would probably be random and unlikely to explain the observed association between active migraine with aura and haemorrhagic stroke and, if present, would probably lead to an underestimation of the effect. Thirdly, we had no further details on migraine aura in this cohort, which would have allowed us to classify participants according to International Headache Society criteria for aura or to take frequency of aura into account. Our prevalence of aura, however, is in the range reported in other population based studies.^{3,51} Fourthly, the Women's Health Study was designed as a randomised controlled trial of aspirin and vitamin E, and specifically for aspirin there is a concern of increased risk of haemorrhagic stroke. In the Women's Health Study, however, neither aspirin nor vitamin E assignment was associated with risk of haemorrhagic stroke,^{28,29} randomised treatment assignments were evenly distributed across migraine groups, and we found no significant effect modification of the association between migraine with aura and haemorrhagic stroke according to randomised treatment assignments. Fifthly, despite adjustment for many potential confounders through a propensity score technique, residual and unmeasured confounding remains possible as our study is observational. Finally, participants in the Women's Health Study were middle aged health professionals, most of whom were white, and thus generalisability to other populations of women might be limited.

Clinical implications

Migraine with aura has been consistently linked with an increased risk of ischaemic stroke and might also be a marker of increased risk for other ischaemic events. Our results extend those previous findings and suggest that migraine with aura might also be a marker for increased risk of haemorrhagic stroke. Because of the relatively low attributable risk (four additional haemorrhagic strokes associated with migraine with aura per 10 000 women per year), however, there are no immediate implications for clinicians or patients other than the evaluation of prevalent cardiovascular risk factors that might influence ischaemic and haemorrhagic vascular events.

Unanswered questions and future research

There are many unanswered questions, particularly involving specifics on migraine aura and biological mechanisms linking migraine with aura to an increased risk of haemorrhagic stroke. The low attributable risk might mean that the increased risk of haemorrhagic stroke is limited to a subgroup of patients with migraine with aura. In addition to studies targeting potential biological mechanisms, future collaborative efforts are needed to study whether migraine aura specifics or the

course of migraine influences risk of subsequent ischaemic and haemorrhagic vascular events.

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Contributors: TK conceived and designed the study, analysed the data, and drafted the manuscript. CSK and JEB were responsible for the acquisition of the data. All authors interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the version to be published. TK is guarantor.

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